4. Responses to Appendix M-II *Description of the Proposal*

M-II-A. Objectives and Rationale: Disease Selection

M-II-A-1. Use of Recombinant DNA for Therapeutic Purposes

Gibbon Ape Leukemia Virus (GALV) pseudotyped replication-defective retroviral vectors encoding an anti HIV-1 ribozyme (RRz2) or control vector (LNL6), will be used to transduce CD34 selected peripheral blood progenitor cells derived from HIV-1+ individuals with a CD4+ T-cell count between 200 and 500/mm^3. Transduced progenitor cells will be re-infused into the patient in the absence of myeloablative therapy. Levels of transduced cells in peripheral blood and bone marrow containing the ribozyme, or control vector, will be assayed by PCR and construct expression by RT-PCR (See Study Protocol).

a. HIV-1 is the recognized etiologic agent for AIDS[1-6]. Progression from the prolonged asymptomatic or "latent" phase of HIV-1 infection to the full blown AIDS syndrome is accompanied by a precipitous decline in CD4+ T-cell numbers as well as hematologic derangement [1-6]. To date, a variety of antiviral therapies, including nucleoside analogues such as AZT, ddI, 3TC, and protease inhibitors, have had only a modest impact on the natural history of disease. Given the lack of satisfactory therapeutic alternatives, newer strategies are required to retard and possibly reverse progression thereby augmenting current therapeutic options.

b. HIV-1+ patients aged 18-55 with CD4+ T-cells > 200/mm^3 and < 500/mm^3, with Karnofsky status > 80%. These patients have at least a 90% survival at 2 years, allowing adequate potential follow-up. We have selected a more advanced population with a HIV-1 plasma RNA copy number (as determined by RNA PCR assay-Roche) of > 10K, < 200 K/ml which allows an objective measure of response that appears to correlate with clinical outcome (2nd ASM National Retrovirus Meeting, Feb 95, Coombs, personal communication). Measures of disease progression include i) viral load as determined by RNA PCR assay, ii) HIV-1 assay by limiting dilution, iii) CD4+ assay by flow cytometry. In addition, since this trial is internally controlled through use of two separately transduced populations (i.e. LNL6, RRz2), additional estimates of efficacy related to relative cell survival may be feasible.

c. This is a Phase I protocol designed to assess feasibility and safety of GALV mediated stem cell transduction, ability to detect transduced cell populations and as an additional aim, relative survival of ribozyme transduced versus control transduced cells. Although such transduction may result in delayed progression, this is specifically a Phase I trial and is not designed to prevent further disease manifestations or progression.

d. Alternative therapies include approved nucleoside and non-nucleoside analogues (e.g., AZT, ddI, ddC, d4T, Nevaripine) as anti HIV-1 reagents. Other experimental alternatives include other gene therapies such as the use of transdominant Rev/antisense, etc. A patient with 200 - 500 CD4+ cells/mm^3 would typically receive a combination of AZT and ddC or experimental D4T or ddI. Experimental therapeutic options might also include use of a protease inhibitor. The advantages of these approaches relative to gene therapy are unknown, but no current treatment strategy is curative. A transient increase in T cell counts and a 12-18 month extension in life expectancy is found with current modalities. The use of oral medication is considerably simpler than stem cell directed gene therapy. However, systemic side effects may be observed including anemia, nausea, bone marrow suppression, pancreatitis and neurologic symptoms.